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POSSIBLE INCIDENCE OF ARBOR VIRUS IN THE ETIOLOGY OF
VIRAL AFFECTIONS IN MEDITERRANEAN FRANCE

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At this time that a study* is being carried out in France regarding the virus types transmitted by arthropods (or arbor viruses, term derived from the English arthropod-borne virus), we feel it is useful, before publication of the first results so obtained, to present for the information of clinicians, a brief review of arbor virus-caused diseases present in the Mediterranean area and which should therefore be sought in the Mediterranean part of France.

We have limited this study only to those arbor viruses which may be encountered in our regions either permanently present or present due to a regular annual reinfection process. We will therefore omit on one hand certain European diseases such as tick encephalitis of Central Europe of which the extension (proved by the laboratory) does not seem to have gone beyond Austria to the West and on the other hand we shall also omit affections of possible but only accidental occurrence such as dengue and yellow fever. These two diseases, in fact, may

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not be developed in epidemic form except when the virus which causes them is introduced (by a viremic patient) in the territory where the vector insects are present at the time of the year during which such insects bite man. These circumstances are exceptional but they may be observed occasionally (yellow fever in Lisbon in 1819, dengue in Greece in 1927); nevertheless, the virus cannot then establish itself in such regions, in other words it is incapable of survival from one season to the next, the epidemic is arrested and the endemic situation may not result from this.

The necessary conditions for the definitive installation or for a seasonal but regular permanence of an arbor virus in a geographic area depend on several factors which are beginning to be better understood. In order for this installation to occur, it is necessary that the "reservoir" animal species be present as well as the "vector" species.

The "reservoir" are the animals which may harbor the virus in a permanent fashion, and have continuous viremia which is of a sufficient level to permit the infection of vectors and also sufficiently prolonged in order to explain the conservation of the virus. The reservoir species may play a role in the introduction of a virus into a country and also in its preservation from one season to the next. These animals are not necessarily sensitive hosts in the strict sense of the word since they may actually not present any sign of clinical disease at all. On the other hand, certain sensitive hosts, in other words animals which react to the contamination with the virus with the occurrence of the clinically detectable disease which may terminate in death, may not present a viremia of sufficient level and duration so as to permit transmission (epidemiologic dead end).

The "vectors" are the biting insects in which, after the sense of the very definition of the arbor virus group, the virus must actively multiply. There is a meal of infective blood which is taken by biting a viremic animal, an incubation phase during which the transmission is impossible (phase of eclipse) and then a period during which, by biting another animal, the vector will inoculate it with the virus.

The existence of animals which may play a role of reservoir for certain arbor viruses is established beyond any doubt in the region of the Mediterranean coastal area; some animals among the known reservoir species (for instance the monkeys) are not among them, but many species of birds, or rodents, of wild and domestic mammals can perfectly well play this role.

With regard to the vectors, the entomologic fauna of this region is very rich so that one can find among it numerous species already proven to have a role in the transmission of arbor viruses (various species of *Culex*, of *Aedes*, of *Mansonia*, of *Ixodes*, etc.) and also other related species may eventually be implicated in the transmission cycle.

Before beginning the study of these viral diseases, we should briefly review what is the essence of arbor viruses. Many of these viruses, the most important ones in human and veterinary pathology, have been known for a long time, but there has been no attempt to relate diseases which seem so different from one another as Japanese encephalitis, yellow fever, tick encephalitis, or the American equine encephalomyelites, for instance. Speculations in this field were limited to discussion of the possible antigenic relationships between the virus of dengue and that of yellow fever transmitted by the same vector. However, while diagnosis of yellow fever became possible by the isolation of the virus in the mouse and serological tests, the diagnosis of dengue, as is well known now, was often made in error.

In 1944, Sabin (1950 publication), after having inoculated human volunteers with serum taken from patients with clinical dengue, including sera taken in Hawaii (dengue I) and in New Guinea (dengue II), succeeded in adapting this virus to the mouse by intracerebral inoculation. Later, Sweet and Sabin (1954) proved that the antigen which developed in the brain of infected mice was capable of agglutinating the erythrocytes of one-day-old chickens and that this antigen could be neutralized by specific dengue antibodies both in the serum on convalescence and in the serum of experimental animals (hemagglutination inhibition test). Casals and Brown (1954), discovering the same hemagglutinating property in the brain of inoculated mice which had been inoculated with various viruses of which the common property was to be neurotropic for the mouse and to be normally transmitted by insects, distinguished two groups among these viruses according to the temperature and the pH which were optimal for hemagglutination, and later also on the basis of serological cross-reactions which were more or less definite between these viruses. In Group A they found in particular the virus of American equine encephalomyelitis, while in Group B, yellow fever, dengue, tick encephalitis and the louping-ill, Japanese encephalitis B, etc.

This classification is currently accepted by all virologists and in addition to Groups A and B we now have Group C which includes viruses isolated in the Amazon valley, Groups Buayamvera, California, etc., and a number of viruses without groups, the total number of counted virus strains being now about 175.

While some of these viruses are definitely pathogenic and of obvious epidemiologic interest, other viruses, isolated from arthropods during systematic studies, are still not related to any specific disease.

Inasmuch as the subject is limited as we have above described, we shall here study only three of these viruses: the West-Nile virus, the three-day fever virus (Naples and Sicily varieties), and the Tahyna virus.

West-Nile Virus

This was isolated for the first time in Uganda in 1937 (Smithburn et al, 1940) from the blood of a female patient with fever, of the Negro race and living in the district of the West Nile. The blood was inoculated into mice intracerebrally one hour after removal from the patient. Since then, the virus has been isolated again in man in Egypt (Melnick et al, 1951, three strains), (Taylor et al, 1956, 23 strains isolated between 1951 and 1954), in Israel (Bernkopf et al, 1953, epidemics of 1951; Goldblum et al, 1954, epidemic of 1952, nine strains isolated), in the Belgian Congo (Lucasse, 1963, one strain isolated in 1958), in South Africa (Kokernot et al, 1959), and finally a second strain has been isolated in Uganda (Woodall, 1962).

The activity of this virus in infecting man is therefore well proved by these repeated isolations carried out both in the south and north of Africa and Israel.

The actual area of presence of this virus may be even larger, but the suspicion is based only on serological examinations which are difficult to interpret because the West-Nile virus, being an arbor virus of the B Group, possesses common antigens with many viruses of this group. Its presence in certain geographic areas (such as Ethiopia) may have been a cause of special difficulty during the course of serologic studies on yellow fever.

Other sources of virus have been isolated from animals:

a) directly from insects: both from mosquitoes *Mansonia metallica* in Uganda (Woodall et al, 1961), *Culex univittatus* and *Culex antennatus* in Egypt (Taylor et al, 1956), *Culex Vishnui* in India (Work et al) and from *Argas hermanni* in Egypt.

b) from birds: in Egypt from a black bird and the rock pigeon (Work et al, 1953), in Israel, in South Africa, from a linnet (captured at the end of April) (Kokernot et al, 1959), in Borneo;

c) from mammals: very recently an isolation of this virus was successful in Egypt from the brain of a horse which died of encephalitis (Schmidt et al, 1963).

This enumeration of the isolated strains and of the circumstances of their isolation may seem somewhat pedantic but it is indispensable because it permits us to conclude that the virus is present in South Africa and through the whole area up to the Nile delta and that it is particularly active during the summer months, that it is present in the middle east where it has caused epidemics in Israel, in India and even in the former Dutch territories of that region where it was isolated from a bird. This area of South Africa, the middle east and India corresponds to a natural route for certain migrating birds. It is logical to believe that the virus may have been carried either in the blood of the bird, or as insect larvae, for instance, of Argas which is a parasite of the bird.

As soon as the virus is planted in a geographic area where there are possible vectors and provided that these are at the phase of their development during which they may bite vertebrates, an epidemic may well take place, the human patient presenting a viremia which is sufficient to infect the vector mosquito (Taylor et al, 1956). But while the route of migration of birds which come from Asia and pass through the valley of the Nile is well known, the migrations of birds between the Nile delta and the Rhone delta have been studied to a lesser extent. The animal species which are implicated in the viral cycle are especially the migrating birds such as the crow and possibly some of the mammals (horses); the most frequent vectors are the Culex mosquitoes. All of these animal species are present and indeed quite abundant in the Mediterranean region of France.

What are the clinical signs of the disease due to the West-Nile virus?

The most definite clinical picture was observed in Israel during the years of 1951 (Berkopf et al, 1953) and 1952 (Goldblum et al, 1954). In this case naturally occurring diseases were in question whereas in the experiences of inoculation of man with virus, carried out by Southam and Moore (1954), the massive doses of virus injected into patients with inoperable cancer with a therapeutic aim in mind may not have faithfully reproduced the evolution and the nature of habitual symptoms. The only practical interest of the latter studies was to show that certain of the cases did produce diffuse or transitory encephalitis, thus confirming the neurotropism in man.

During the course of epidemics in Israel, observed between July and September of 1951 to 1952, the beginning of the disease, after a period of incubation which seemed to be from three to six days, was quite sudden, the temperature rapidly increasing up to 40°C. In the majority of cases, the fever remained for three days, then gradually the temperature fell during the course of the following days in order to be back to normal between the seventh and ninth days. Goldblum has observed in about one case in ten, recurrence which took place one to three days following the first attack, the recurrence lasting from three to five days during which there was a return of the symptoms in a somewhat attenuated form. A moderate degree of bradycardia was often observed during the moment of the fall of the temperature curve.

In nearly all of the adults (about 80 percent) and in somewhat fewer than 40 percent of the children there were present severe frontal headaches with painful movement of the eyeballs. Muscular pains were also a consistent symptom and some of the patients (20 percent) had intestinal difficulties. Nausea and anorexia were more frequent in the adults while emesis was primarily found in children.

Many of the patients, especially the children, had, during the first three days of the disease, maculo-papular rash starting in the trunk and extending sometimes toward the head and extremities; this rash persisted a few days and was not followed by desquamation. The hemogram showed little change, although there was always a moderate leukopenia with a relative lymphocytosis.

Some lymphadenitis was frequently observed, especially among adults, with swelling either of a single lymph node or of the cervical axillary or inguinal chain of lymph nodes (moderate swelling of the size of a pea to that of a cherry). This adenitis persisted during the course of convalescence and could even be noted during the two months following the disease.

Neurologic signs were seen in some cases as symptoms of meningeal irritation, with the Kernig sign positive. These seemed more frequent in children (one in seven).

In addition to this typical picture, certain symptoms may be more or less frequently noted according to the specific epidemic.

In 1952, Goldblum noted a frequent congestion of the face with conjunctival injection. In 1951, Bernkopf found in some cases signs of an upper respiratory inflammation of a relatively pronounced degree, since two of the patients were even

suspected of having diphtheria. Finally, in 1952, Goldblum reported in a few cases moderate splenomegaly.

The disease evolves toward cure without sequelae but convalescence, especially in the adult, is accompanied by easy fatigability and fatigue persisting for several weeks.

If this description of epidemic disease is compared with the cases noted in children in the endemic zone (Taylor et al, 1956), we find that clinical signs are essentially identical despite a somewhat lesser percentage of certain specific symptoms. Out of 22 Egyptian children who definitely had an infection with the West-Nile virus (with virus isolation in each of the cases), 5 presented a rash with fine papules and only 3 had a moderate degree of lymphadenitis. In general, fever persists from five to six days and no neurologic sign was noted.

Finally, we report a case of accidental laboratory infection (Hamilton and Taylor, 1954), which was characterized especially by muscular pains and relatively severe lymphocytosis.

Every year in Camargue there are found more or less frequent cases of fever in some of which a mild meningeal affection is present, a disease which is known there under the name of Camargue fever. It is probable that some of these cases are due to enterovirus (Coxsackie in particular), but it must also be considered that virus of the West-Nile is one of the possible viruses in question, inasmuch as the clinical picture of this disease is quite similar to the one we have just described.

It is obvious that all these symptoms, in the absence of a definite epidemic, are only indicative and do not usually permit a definite diagnosis of the disease in the absence of laboratory confirmation. The final certainty of diagnosis can only be made by the laboratory.

On the other hand, these symptoms are so common that they may also well be attributed to other causes and the presence of this virus in a region where it has not previously been known to exist may well pass unnoticed.

In the Mediterranean area (especially in Egypt) the fever due to the West-Nile virus may be especially easily confused with the phlebotome fever or the three-day fever.

Three-Day Fever or Phlebotome Fever

In contrast to the fever due to the West-Nile virus, the study of which was clinically possible due to the preliminary

Isolation of the virus, the phlebotome fever or fever of the three days was clinically identified quite a long time ago since the very first description is due to Pym (1806). In 1905, Taussig suspected the phlebotome to be the vector of this disease and Doerr et al (1909) proved it is a viral disease by inoculation of volunteers with the filtered serum of patients.

In spite of this fact, the clinical description is not always the same depending on the authors, which may be due both to variation of each epidemic and possibly to the easy confusion with other viral affections which are not yet quite identified and which may occur in such epidemics.

The most characteristic epidemics seem to have been observed among military personnel who habitually live outside of the Mediterranean area and were assembled during the course of wars on one of the Mediterranean islands, particularly the island of Malta. These epidemics have broken out among English troops sent to Crimea (1855-1856) and in Sicily during the debarking of the American troops in 1943 (10,000 cases).

During the Sicilian epidemic, 100 volunteers were inoculated (Sabin et al, 1944) with serum of patients. The majority of the symptoms which were noted at the time were of the classical disease.

After an incubation period of three to six days, the start of the disease is quite sudden, sometimes preceded by a sensation of malaise, then the following symptoms may supervene, rarely all observed in the same patient: intense frontal or orbital headache, pain during movements of the eyes and photophobia, general sensation of malaise with rigidity of the neck and the back, with lumbar and sacroiliac and articular pains. The anorexia is generally complete, often accompanied by nausea and sometimes with emesis. Initially, constipation is more frequent while diarrhea supervenes toward the end of the disease and during convalescence. Throat pains of some degree are frequent and occasionally there is also seen epistaxis. Chills are frequent at the beginning of the disease and during the course of the first two days of fever.

Sweating is profuse and vertigo is habitual throughout the course of the disease, with sensations of intense fatigue, especially in the course of convalescence.

Clinical examination reveals striking congestion of the face and neck which may be so pronounced that it makes one think of a sunstroke. The conjunctiva are injected, and the roof of the mouth and the pharynx are congested. There is no

symptom of rhinitis nor of the affection of upper respiratory system. There are no signs of meningitis. The skin is hot but rash is rarely present. There is no lymphadenitis.

The eruption of the face and neck has not been noted in volunteers, but it persists in 40-50 percent of the cases following the fall of the fever as was noted earlier by Castellani (1917), during the course of an epidemic.

The cerebrospinal fluid is normal and the changes in the hemogram are constant: leukopenia especially with lymphocytopenia during the first day, then progressive fall of the neutrophilic polynuclears and increase in the number of lymphocytes during the course of the following days so that at the time of the fall in fever we have a leukopenia with relative lymphocytosis.

The recurrences already noted during the course of epidemics have been found in five percent of the volunteers, with single or multiple recurrences which definitely seem to be due to the virus.

When this clinical picture is compared to that of the West-Nile virus fever, we see that when the disease is typical and particularly during the course of epidemics due to one or the other of the viruses, clinical examination should permit at least orientative diagnosis.

Actually, although many of the symptoms are common to both infections, as they are actually common also to other viral infections, there are nevertheless some important differences.

Thus, for instance, while the rash with maculo-papular eruption starting from the trunk and later extending is more specifically due to the West-Nile fever, the fever of three days produces the intense congestion of the face and neck reminiscent of a sunburn.

Furthermore, while participation of the lymphatic system with single or multiple lymphadenitis persisting after the disease is seen in the West-Nile virus fever; this is not seen in the three-day fever.

The West-Nile virus is neurotropic and may cause in some cases light meningeal reactions although these are quite definite with nuchal rigidity modifications in the C.S.F., light augmentation of the number of blood cells and increase in the protein levels which is not noted ever in the three-day fever where the stiffness of the trunk and neck are due not to a meningeal but merely to a muscular affection.

Finally, the heat and the dryness of the skin are more definite in the three-day fever.

The two infections are quite easily distinguished in the laboratory because the two respective viruses do not have any common antigen, in fact there is no common antigen even among the two different varieties of the three-day fever, the Naples and the Sicily variety.

The virulent serum which was used to infect volunteers Sabin et al (1944) and which was collected either in the Middle East, Palestine and Egypt, or in Sicily in 1943, permitted showing the identity of the virus with crossed immunity tests (Sabin, 1951); however, a second epidemic broke out in Naples in 1944 during the course of the American landings in Italy and the serum was taken from patients who were then in the acute phase of the disease.

Following nine years of frozen storage of the virulent serum of Sicilian origin and eight years of preservation of the serum taken in Naples, Sabin succeeded in passing and adapting this virus to the suckling mouse inoculated intracerebrally (Sabin, 1955). At this time, he was able to demonstrate that the Naples and Sicily varieties were antigenically different, although both were transmitted by the *Phlebotomus papatasi*, and although both produced an identical clinical syndrome of the three-day fever.

Later, both of the strains were isolated by Taylor (1958) during systematic studies carried out in five villages situated about 30 kilometers north of Cairo during the years 1951 to 1954. He isolated 19 strains from Egyptian children and 3 strains from American adults. Of these, 20 strains were of the Sicily variety and 2 of Naples.

A few years later, between June and November 1959, Schmidt et al (1960) were successful in capturing over 30,000 phlebotomes in large apartment houses of the northern suburb of Cairo. For anyone who knows the difficulties in catching phlebotomes, this is in itself quite a success. But, in addition to this, these insects were identified one by one, which is certainly a very considerable task inasmuch as this identification is possible only by a microscopic examination between the large and small blades of the pharyngeal structure of the insect, the head being separated from the body and the body then being collected together in pools after identification so as to try to isolate the virus.

Nearly all of the captured phlebotomes which were identified were of the *Phlebotomus papatasi* species and out of 59

inoculated pools, the authors were able to isolate four strains, all of them of the Sicily variety, three of the strains having been isolated in August and one in October.

Thus, it has been proved that the three-day fever is transmitted by the *Phlebotomus papatasi*. This has been definitely proved for the Sicily variety and it is quite likely for the Naples variety. On the other hand, the nature of the animal reservoirs is completely unknown.

In France in the Mediterranean south, phlebotomes are quite numerous in certain regions; *Phlebotomus papatasi* is present but does not seem to predominate (Houin, 1963).

On the other hand, from what is known by now of the clinical syndromes caused by the West-Niles virus and by the virus of the three-day fever, and also of the difficulty which clinical diagnosis causes, it would seem indispensable to look systematically for biological proofs of the presence of this disease before claiming that it is present.

In the thesis of Risse (1941), 25 cases were reported in the Montpellier region, but a careful study of his observations does not convince one that we are really dealing here with phlebotome fever.

Only laboratory studies, starting from the well-known virus strains, will permit determination of the incidence of the three-day fever in the Mediterranean area.

Tahyna Virus

The Tahyna virus is one of the newest arbor viruses isolated from mosquitoes during the course of recent years in Europe (Bardos et al, 1959). These isolations were carried out between the month of July and the month of August 1958 from *Aedes vexans* (three strains) and *Aedes caspius* (two strains) captured in eastern Slovakia. In August 1960, three additional strains were isolated in southwestern Slovakia from *Aedes vexans*. These isolations were made by inoculating mosquito *embryos* intracerebrally to suckling mice. This virus, which resembles the arbor viruses, is actually similar in regard to its immunologic properties to the California group (of which the typical representative is the California encephalitis virus) (Casals, 1962); it has been studied comprehensively by Bardos et al at the Institute of Epidemiology and Microbiology of Bratislava.

The habitual vectors, *Aedes vexans* and *Aedes caspius*, common mosquitoes are distributed in a large geographical zone.

Reservoir species have been sought in Czechoslovakia: birds do not seem to play a role, at least not a role of any importance inasmuch as they do not show any viremia and do not keep the virus after experimental infection. Unless the inoculum is quite considerable, they do not produce any antibodies. In addition, serological study of numerous species of birds did not reveal the presence of antibodies in these animals. The subclinical infection does not appear in swine after injection of the virus and production of antibodies ensues, but the level of viremia is insufficient to permit the transmission of the virus. On the other hand, in rodents such as the rabbit and the hare, as well as the hamster, a viremia does occur for three or four days at a relatively high level; this is then followed by the production of antibodies without appearance of clinical signs. These animals are also frequently bitten by Aedes mosquitoes, and they would seem to represent the most probable host reservoir to the extent that it can be shown by these studies carried out in Czechoslovakia. On the other hand, other animals may also be suspected of playing a role, inasmuch as serologic studies proved the presence of specific antibodies in horses and cattle as well as in swine and in rodents.

The geographic distribution of the virus has been studied in man by serologic studies. Antibodies are frequently found in the sera of inhabitants of Czechoslovakia, Austria, Hungary, while they are more rare in Finland and Yugoslavia and Italy (Bardos et al, 1961). In the first group of these countries, the percentage of positive reactions is between 30 and 60 percent of the population; in the second group, it is between 2 and 9 percent. However, in the centers of the foci, it is possible to find very high percentages, going up with the age of the inhabitants and sometimes reaching among adults even figures as high as 96 percent.

This is the first argument in favor of the role of the virus in causing human disease. The second argument is the finding (Bardos and Sluka, 1963) according to which in a number of patients studied in Slovakia and Moravia between June and October 1960, neutralizing the hemagglutination inhibiting antibodies appeared or increased in titer significantly during the course of the affection. These patients have had a feverish disease with headaches, nausea, anorexia and cough; in some of these patients, a pulmonary clinical and radiologic affection was noted. These signs permitted identifying with more precision the pathogenic role of the virus. Finally, Likar and Casals (1963) isolated two strains of a virus analogous to the Tskyna, the Trojica virus starting from 5,000 specimens of sera in 1960 and 1961 in Slovenia (Yugoslavia) from apparently healthy persons. It would thus seem that the virus is capable

of producing subclinical infections or of persisting for a long period of time in the blood of infected persons.

Although the role of the Tahyna virus in human pathology is not established in detail, its presence should be sought in our regions since all conditions which seem necessary for its activity are present here.

At the time that we are beginning an epidemiologic study of this type in order to detect in a region the presence of some type of virus which had never been isolated previously, it is logical to first look for a lead. This lead may be in our case the geographical, climatic and animal relationship of the Mediterranean southern France with that of other territories which border on the Mediterranean Sea and where the arbor viruses are present. Why, indeed, should this virus never have penetrated into France since in its cycle there are certain species of birds, mammals and mosquitoes which are present in France? It is not even necessary to take into consideration the modern extension of rapid transportation including planes or the displacements of populations and armies since the natural route of animal migrations already have been following certain definite patterns across and over the sea. Since we know that migrating birds which fly across the Mediterranean frequently carry with them grains which insure the dissemination of certain plants as well as of the parasites which are possible vectors, it is very hard to conceive of any type of public health guard which might prevent diffusion of the viruses which such animals may carry with them.

On the other hand, the fact that the introduction of the arbor viruses is possible and the fact that the transmission from animal to animal and eventually to man is equally possible, still do not suffice to prove the presence of this virus in France: it is precisely the aim of the study to prove such an introduction.

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